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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,254	ADDERSON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *17-32,38-55 and 61-67* is/are withdrawn from consideration.

5)☒ Claim(s) *56* is/are allowed.

6)☒ Claim(s) *1-16,33-37 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election

1) Acknowledgment is made of Applicants' election filed 12/06/04 in response to the written lack of unity mailed 10/22/04. Applicants have elected invention I, drawn to the nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, with traverse. Applicants request that the lack of unity requirement be withdrawn in its entirety. Applicants further request that, at a minimum, inventions I, III and V as well as inventions II, IV and VI respectively, should be regrouped and examined together. Applicants in essence argue that the restriction set forth in the instant application is improper under PCT rules 13.1 and 13.2 and under the USPTO's policies for the examination of national phase applications including nucleotide sequences. Applicants submit that rule 13.2 may at best reasonably support a requirement to subdivide the instant claims into two distinct groups based upon the special technical features of the amino acid sequence of SEQ ID NO: 2 and 4. Applicants cite section 1850 of MPEP and state that up to ten nucleotide sequences that do not have the same or corresponding special technical feature are permitted in an application.

Applicants' arguments have been carefully considered. Upon further consideration, the following modified lack of unity of inventions is set forth in the instant application.

Invention I: Claims 1-16, 33-37 and 56-60, drawn to an isolated nucleic acid molecule coding for the amino acid sequence of SEQ ID NO: 2; a vector and a host cell comprising the same; a protein comprising the amino acid sequence of SEQ ID NO: 2 and a vaccine comprising the same; and a method of immunizing against Group B streptococcal infection by administering the vaccine.

Invention II: Claims 17-32, 38-40 and 61-67, drawn to an isolated nucleic acid molecule coding for the amino acid sequence of SEQ ID NO: 4; a vector and a host cell comprising the same; a protein comprising the amino acid sequence of SEQ ID NO: 4 and a vaccine comprising the same; and a method of immunizing against Group B streptococcal infection by administering the vaccine.

Invention III: Claims 41-55, drawn to a diagnostic method of determining infection or colonization of a mammal by virulent GBS comprising analyzing a bodily fluid or culture for the presence of one or more gene products specific to type III-3 GBS.

The special technical features of inventions I and II are nucleotide sequences encoding SEQ ID NO: 2 and SEQ ID NO: 4 respectively. These two genes do not share significant common structural elements. The special technical feature of invention III is a diagnostic method of determining infection or colonization of a mammal by virulent GBS comprising analyzing a bodily fluid or culture for the presence of one or more gene products specific to type III-3 GBS (see base claim 41). However, such a method is already taught in the prior art. For instance, Takahaski *et al.* (*J. Infect. Dis.* 177: 1116-1119, 1998) taught a method of analyzing a blood or CSF sample, or a culture from female human patients for the presence of DNA products specific to type III-3 GBS, wherein the positive results of the method indicate the infection of the mammal by virulent GBS (see abstract; Materials and Methods; Results; and page 1119). Takahashi's method inherently involves the step of collecting a blood or CSF from the patient and inherently serves as a diagnostic method for determining whether a mammal is infected by virulent GBS. The special technical feature of invention III does not define over the prior art and therefore is not a unifying feature.

Status of Claims

2) Claims 1-67 are pending.

Claims 17-32, 38-55 and 61-67 have been withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-16, 33-37 and 56-60 are under examination. A First Action on the Merits on these claims is issued.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' Information Disclosure Statement filed 08/22/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

4) Acknowledgment is made of Applicants' submission of raw Sequence listing and CRF which have been entered on 07/09/02.

Priority

5) The instant application is a national stage 371 application of PCT/US00/17082, filed 02/21/2000 and claims priority to the provisional application, 60/140,084, filed 06/21/1999.

Rejection(s) under 35 U.S.C. § 101

6) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

7) Claims 6, 14 and those dependent therefrom are rejected under 35 U.S.C § 101 as being directed to a non-statutory subject matter.

Instant claims are drawn to a host cell, and therefore read on products of nature, i.e., naturally occurring bacterial cells. The claims lack limitations, which distinguish this product from those that may exist naturally. Consequently, the claims do not embody patentable subject matter as defined in 35 U.S.C § 101. See MPEP 2105. Products of nature are not patentable because they do not reflect the 'hand of man' in the production of the product or manufacturing process. *Diamond v, Chakrabarty*, 206 USPQ 193 (1980). The rejection can be overcome by amending the base claims to recite --An isolated host cell-- in connection with the product to reflect the hands of the inventors in the production or creation of the recited product, if descriptive support for such a limitation exists in the specification, as originally filed.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

8) Claims 33-37 and 57-60 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, claim 57 encompasses a vaccine comprising an isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 2 for immunizing a mammalian host against virulent Group B streptococcal infection. Claims 33-37 encompass a method of immunizing a mammal against Group B streptococcal infection comprising administering to the mammal a vaccine comprising an immunologically effective amount of a recombinantly produced protein comprising the amino acid sequence of SEQ ID NO: 2, with or without the protein of SEQ ID NO: 4 which is also recombinantly produced. The term 'vaccine' by definition requires that the claimed element in the vaccine elicit a protective immune response, humoral and/or cell mediated, in a suitable host who is susceptible against pathogens that produce or carry such element. In the instant case, the active element in the vaccine is a protein of the amino acid sequence, SEQ ID NO: 2, which is required to be protective against a Group B streptococcal infection. The phrase 'Group B streptococci infection' broadly encompasses GBS types I, II, III, V, VIII etc. A review of the instant specification indicates the following. At page 7, the specification states that: (a) The *spbl* gene product 'may stimulate an immune response' when administered to a host; (b) Recombinantly produced proteins are especially desirable, as they can be produced in large amounts and purified; (c) Recombinantly produced proteins 'may' be engineered to maximize desirable activities and to minimize unwanted effects; and (d) The recombinantly produced *spbl* and/or *spb2* gene products 'may be' used as carrier proteins for a polysaccharide-protein or oligosaccharide-protein conjugate vaccine. At page 12, the specification states that *spbl* is not a member of a significantly homologous "family" of genes. It is further stated that the 53 kD protein is a predicted protein product having the characteristics of a typical gram positive cell-wall bound protein. Based on segmental homology alone with *Actinomyces* fimbrial proteins and *H. influenzae* HMW1, the specification speculates that 'Spb1 might contribute to GBS adhesion or invasion'. Applicants state that a *spb1*⁻ isogenic deletion mutant GBS strain was created by homologous recombination and that the number of *spb1*⁻ bacteria adherent to A549 monolayers was reduced by 60.0% and the number of intracellular invading bacteria was reduced by 53.6%. With this, Applicants conclude that 'Spb1 may contribute to the pathogenesis of GBS pneumonia and bacterial entry into the blood stream'. However, there is no showing within the instant specification that a protein comprising the amino acid sequence of SEQ ID NO: 2 was indeed produced, isolated and purified, that too recombinantly produced, such that an immunologically effective amount of the same served as a 'vaccine'. The 53

kD protein is described as the predicted spb1 protein product (see page 12). There is absolutely no showing that a 'recombinantly produced protein comprising the amino acid sequence of SEQ ID NO: 2' or an 'isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 2' was administered to any mammal as a vaccine wherein the vaccine provided 'protection' against, or reduced the mortality or morbidity of the disease caused by, pathogenic GBS in said mammal. This is critically important because it is well known in the art that, of a myriad of polypeptides that may be produced by a bacterial or microbial pathogen, not all polypeptides elicit a pathogen-specific immune response that is protective against the pathogen. The art of vaccines recognizes the unpredictability associated with whether or not an antigen or immunogenic component derived from a microbial pathogen is immunoprotective. For instance, Ellis RW (*Vaccines*, (Eds) Plotkin *et al.*, W.B. Saunders Company, Philadelphia, Chapter 29, 568-575, 1988, see page 571, second full paragraph) reflected this problem in the teaching that the key to the problem of vaccine development "is the identification of that protein component of a ..... microbial pathogen that itself can elicit the production of protective antibodies ..... and thus protect the host against attack by the pathogen". It is emphasized that predictability or unpredictability is one of the *Wands* factors for enablement. In the instant case, the claimed protein, in isolated, purified or recombinant form, is not evaluated for its protective capacity against any GBS infection using an art-accepted *in vivo* animal model, nor are there any *in vitro* test results correlative of protection against any GBS infection. Furthermore, the protective nature of a recombinantly produced bacterial protein is not predictable. The art recognizes the unpredictability associated with the protective ability of a recombinantly produced bacterial protein. For instance, Manetti *et al.* (*Infect. Immun.* 63: 4476-4480, November 1995) explicitly demonstrated that a recombinant *Helicobacter pylori* CT protein "lacked any biological activity" and failed to induce antibodies that are neutralizing. Such a recombinant protein would be unlikely to have the ability to induce useful antibodies to virulent GBS and is unlikely to serve as a prophylactic or therapeutic vaccine. Absent a concrete showing that the claimed product is effective in protecting against any GBS infection in any mammal, or eliminate or reduce morbidity and/or mortality due to GBS infections, the claims drawn to a vaccine and method administering the vaccine against GBS infection are considered non-enabled. Therefore, undue experimentation would have been required by one of skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed

due to the lack of specific and adequate disclosure, the lack of working examples, the art-demonstrated unpredictability, the quantity of experimentation necessary, and the breadth of claims. *Ex parte Foreman*, 230 USPO 546, 547 (Bd. Pat. Appls. and Inter. 1986). The claims are viewed as not meeting the enablement provisions of 35 U.S.A. § 112, first paragraph.

9) Claims 6-8 and 14-16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated or cultured cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are evaluated based on the *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The specification at first full paragraph on page 8 discloses that the '*spbl* and/or *spb2* genes may also be introduced into a mammal using either naked DNA or other gene therapy techniques to induce an immune response against virulent GBS'. However, the specification does not teach any methods or working examples that the *spbl* gene is introduced and expressed in a host cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vectors would introduce the *spbl* gene into the host cell and in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A. *J Pharm Pharmacology* 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed

(see paragraph 1 of page 1170 of Phillips). Phillips also states that the problem with gene therapy is two-fold: (a) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and (b) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (see paragraph 1 of page 1170). Therefore, undue experimentation would have been required by a skilled artisan to introduce and express the *spbl* gene of the instant invention into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express successfully the *spbl* gene of the instant invention in the cell of an organism or be able to produce the gene product protein in that cell.

The specification at first paragraph on page 6 of the instant specification states that a nucleic acid molecule of the present invention may be operably linked to expression control sequences, which expression control sequences collectively provide for the replication, transcription and translation of a coding sequence in a recipient cell or an appropriate host cell. A 'host cell' as recited in claims 6-8 and 14-16 encompasses a mammalian cell, embryonic cell, multicellular animal cell or transgenic cell. However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated *spb1* gene of SEQ ID NO: 1 is demonstrated to express the *spb1* gene product of SEQ ID NO: 2. The unpredictability is *very high* with regards to making transgenic animals. For example, Wang *et al.* (*Nuc. Acids Res.* 27: 4609-4618, 1999) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene (see page 4617).

Due to the large quantity of experimentation necessary to successfully introduce and express the *spbl* gene of the instant invention in a host cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the *spbl* gene in to the host cell of an organism to be able produce the gene product, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of transferring genes into an organism's cells, and the breadth of the claims, undue experimentation would have been required to make and/or use the claimed invention in its full scope. Applicants should note that this rejection could be overcome by amending the claims to recite, for example, --An isolated host cell...--, if descriptive support for such a limitation exists in the specification, as originally filed.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

10) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

11) Claims 1-16, 33-37 and 57-60 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) In claim 1, for clarity and for the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation 'comprising nucleotides which code for' with the limitation --encoding--.

(b) Claims 33 and 57 are confusing and/or incorrect in the limitation: 'streptococci infection'. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --streptococcal infection--.

(c) Claims 2-16, 34-37 and 58-60, which depend directly or indirectly from claim 1, 33 and 57 respectively, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

12) Claims 1-16, 33-37 and 57 stand rejected. Claim 56 is allowed.

13) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (571) 273-8300.

14) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

15) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

February, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER